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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/245,603      | 02/05/1999  | DAVID T. CURIEL      | D6080               | 5072             |

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EXAMINER

PARAS JR, PETER

ART UNIT

PAPER NUMBER

1632

DATE MAILED: 11/23/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

Application No.

09/245,603

Applicant(s)

CURIEL ET AL.

Examiner

Peter Paras

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☒ Responsive to communication(s) filed on 28 August 2001.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 1-4, 6-9, 11, 12, 16, 18-20, 22 and 23 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-4, 6-9, 11, 12, 16, 18-20, 22 and 23 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 05 February 1999 is/are: a) ☐ accepted or b) ☒ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.  
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

## Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☐ All b) ☐ Some \* c) ☐ None of:  
1. ☐ Certified copies of the priority documents have been received.  
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).  
\* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).  
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

## Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) \_\_\_\_\_
- 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_

***Continued Prosecution Application***

The request filed on August 28, 2001 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/245,603 is acceptable and a CPA has been established. An action on the CPA follows.

Applicant's amendment filed on July 18, 2001 has been entered. Claims 13-15 have been cancelled. Claims 1-4, 6-9, 11-12, 16, 18-20, and 22-23 are pending and are under current consideration.

***Claim Rejections - 35 USC § 112, 1<sup>st</sup> paragraph***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 6-7, 16, 18-20, and 22 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an adenovirus comprising an insertion of a ligand comprising the sequence CDCRGDCFC, the FLAG octapeptide or the RGD peptide into the HI loop of the fiber protein and a method of using the said adenovirus for methods *in vitro*, does not reasonably provide enablement for an adenovirus comprising any modification of the HI loop of the fiber protein and methods of using the virus in methods *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The rejection of

claims 1-4, 6-7, 16, 18-20, and 22 is maintained for the reasons advanced in the Office action mailed on 2/28/01 on pages 2-3.

Applicant's arguments have been fully considered but they are not persuasive. Applicants have argued that the state of the art enables one of ordinary skill in the art to introduce a ligand into the HI loop of the fiber protein without adverse effects on the folding/binding of the fiber protein. Applicants maintain that insertion of a ligand into the loop regions of the fiber protein would not affect folding/binding of the fiber protein because the structure of the fiber knob domain is known and the positions of non-conserved amino acids not involved in forming proper fiber protein secondary structure are known. Applicants also argue that modifications in the HI loop can enhance gene transfer into primary tumor cells. See pages 2-5 of the amendment.

In response, the Examiner maintains that the instant specification has only enabled two modifications of the HI loop domain of the fiber knob, insertion of a FLAG octapeptide and insertion of an RGD peptide. The claims however, are directed to any modification of the HI loop domain of the fiber knob even as the specification has discussed the importance of not interrupting the trimerization of the fiber (see pages 6-8). The Examiner maintains that it is unpredictable if the insertion of other sequences into the fiber knob would affect folding of the fiber knob and allow trimerization. See the Advisory action mailed on 8/13/01 and the Office action mailed on 2/28/01 on pages 2-3. The Examiner maintains that the examples described by the specification have taught specific modifications of the HI loop for enhancement of gene transfer. It is maintained that it is unpredictable if any modification introduced into the HI loop domain

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of the fiber knob can enhance gene transfer into primary tumor cells. Support for the Examiner's assertion can be found in Wickham et al (US 5,46,782, see column 3) who teach that "simply incorporating a known peptide motif into the fiber protein of an adenovirus may not be enough to allow the virus to bind and effectively transduce a target cell". Wickham goes on to report that the effectiveness of the inserted peptide in redirecting virus binding to a cellular receptor is dependent on multiple factors that include "the availability of the peptide motif to bind to the cell surface binding site, the affinity of the peptide motif for the cell surface binding site, and the number of target binding sites (e.g., receptors) present on the cell targeted for gene delivery". For example, if the peptide motif is buried with the structure of the fiber protein, and/or masked by the surrounding structure of the protein, the peptide motif will not be able to interact with and bind its target. See lines 22-27. Furthermore, Wickham discusses that it is the affinity of the peptide motif for the cell surface binding site which determines how efficiently the virus can initiate and maintain a binding contact with the target receptor, resulting in cell infection/transduction. See lines 27-32. The instant specification has not provided any guidance, relevant teachings, or working examples that demonstrate or otherwise correlate the insertion of ligands other than FLAG, RGD or CDCRGDCFC with proper folding that allows trimerization of the fiber protein and enhancement of gene transfer into primary tumor cells. It is further maintained that determination of the effects of particular modifications are not predictable until they are actually made and used; the introduction of any other ligand into the HI loop of the fiber protein is nothing more than a trial and error situation.

Accordingly, the previous rejection is maintained for the reasons of record and as discussed in the preceding paragraphs.

Claims 9, 11-12 and 23 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The rejection of claims 9, 11-15, and 23 is maintained for the reasons advanced in the Office action mailed on 2/28/01 on pages 4-5.

Applicant's arguments have been fully considered but they are not persuasive. Applicants argue that the method of killing tumor cells by administering the claimed adenovirus comprising a ligand inserted into the HI loop of the fiber protein and a nucleotide sequence encoding HSV-TK followed by ganciclovir treatment is a standard treatment procedure. Applicants assert that in light of such the claims are fully enabled.

In response, the Examiner maintains that any modification of the HI loop encompassed in the instant claims is unpredictable with respect to trimerization, folding/binding properties, and cell entry. See above. It is further maintained that the art of gene therapy was unpredictable at the time the claimed invention was filed and has remained so thereafter. See Verma, Eck, and Sandhu as referenced in the advisory action mailed on 8/13/01 and pages 4-5 of the Office action mailed on 2/28/01. The instant specification has not provided any working examples that demonstrate or otherwise correlate to enhanced cellular uptake of the claimed adenoviral vector

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comprising a nucleotide sequence encoding HSV-TK and further comprising any modification of the HI loop with killing of tumor cells *in vivo*.

Accordingly, the previous rejection is maintained for the reasons of record and as discussed above.

***Claim Rejections - 35 USC § 112, 2<sup>nd</sup> paragraph***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The previous rejection of claims 13-15 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is moot as the claims have been cancelled.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1-4, 6-9, 16, 18-20, and 23 as originally filed or amended are rejected under 35 U.S.C. 102(e) as being anticipated by Wickham et al. The previous rejection

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is maintained for the reasons of record advanced in the Office action mailed on 2/28/01 on pages 5-6.

Applicant's arguments have been fully considered but they are not persuasive. Applicants have argued that Wickham et al has not taught the generation of a modified adenovirus that mediates gene transfer to primary tumor cells. Applicants argue that Wickham has not taught modifying an adenovirus by insertion of a ligand into the HI loop. See pages 8-9 of the amendment.

In response the Examiner maintains that Wickham anticipates the instant claims. Wickham has taught modifications in the HI loop (see column 8), wherein the modifications can be insertion of nucleic acid sequences encoding a CDCRGDCFC or RGD peptide (see columns 9, 27, and SEQ ID NO: 3). Wickham et al has taught an adenoviral vector comprising a nucleic acid sequence encoding HSV-TK (see column 14). Finally, Wickham has taught gene transfer into tumor cells. See column 17. See the advisory action mailed on 8/13/01 and the Office action mailed on 2/28/02 on pages 5-6.

Accordingly, it is maintained that Wickham anticipates all of the instant claim limitations for the reasons of record and as discussed in the preceding paragraph.

### **Conclusion**

**No claims are allowed.**



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Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Peter Paras, Jr., whose telephone number is 703-308-8340. The examiner can normally be reached Monday-Friday from 8:30 to 4:30 (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda, can be reached at 703-305-6608. Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center numbers are (703)308-4242 and (703)305-3014.

Inquiries of a general nature or relating to the status of the application should be directed to Kay Pinkney whose telephone number is (703) 305-3553.

Peter Paras, Jr.

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